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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *
* * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

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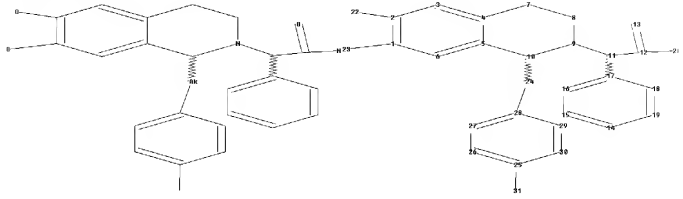

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11  12  13  20  22  23  24  31
ring nodes :
1  2  3  4  5  6  7  8  9  10  14  15  16  17  18  19  25  26  27  28  29  30
chain bonds :
1-23  2-22  9-11  10-24  11-17  11-12  12-13  12-20  24-28  25-31
ring bonds :
1-2  1-6  2-3  3-4  4-5  4-7  5-6  5-10  7-8  8-9  9-10  14-15  14-19  15-16  16-17
17-18  18-19  25-26  25-30  26-27  27-28  28-29  29-30
exact/norm bonds :
1-23  2-22  4-7  5-10  7-8  8-9  9-10  9-11  10-24  12-13  12-20  24-28
exact bonds :
11-17  11-12  25-31
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  14-15  14-19  15-16  16-17  17-18  18-19  25-26  25-
30  26-27  27-28  28-29  29-30
isolated ring systems :
containing 1 : 14 : 25 :


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:CLASS  12:CLASS  13:CLASS  14:Atom  15:Atom  16:Atom  17:Atom  18:Atom  19:Atom
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30:Atom  31:CLASS




L1      STRUCTURE UPLOADED

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L1              STR
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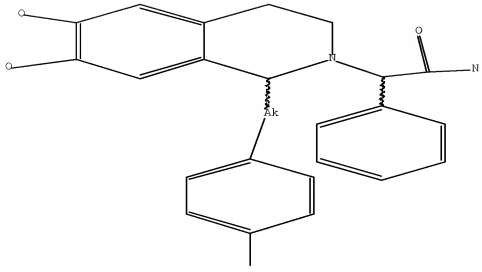

Structure attributes must be viewed using STN Express query preparation.

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=> s l1 full
L3            39 SEA SSS FUL L1

=> file caplus

=> s l3
L4           10 L3

=> s l4 and pd<march 2004
      24837158 PD<MARCH 2004
                 (PD<20040300)
L5            0 L4 AND PD<MARCH 2004

=> dis l4 1-10 bib abs fhitstr

L4   ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2009 ACS on STN
AN   2009:827322  CAPLUS  Full-text
DN   151:148150
TI   Process for the preparation of an enantiomeric trisubstituted
     3,4-dihydroisoquinoline derivative
IN   Bappert, Erhard; De Vries, Andreas Hendrikus Maria; Domin, Doris; Helms,
     Matthias; Imboden, Christoph; Nazir, Zarghun; Skranc, Wolfgang; Spindler,
     Felix; Stanek, Michael; Tschebull, Wilhelm; Verzijl, Gerardus Karel Maria
PA   Actelion Pharmaceuticals Ltd, Switz.
SO   PCT Int. Appl., 34pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     --------------      ----   --------    -------------------    --------
PI   WO 2009083899        A2    20090709    WO 2008-IB55504        20081223
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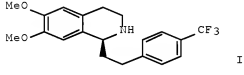
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRAI WO 2007-IB55335 A 20071228

OS CASREACT 151:148150

GI



I

AB The invention relates to a process for the preparation of the compound of formula I by enantioselective hydrogenation of the corresponding imine intermediate catalyzed by bis[chloro-1,5-cyclooctadiene-iridium] and (S)-1-dicyclohexylphosphino-2-[(S)-α-(dimethylamino)-2-(dicyclohexylphosphino)benzyl]ferrocene. Reaction conditions, such as additives, ratios of substrate/catalyst and solvent systems, play roles respect to enantioselectivity and yields therefore were examined Other metal/chiral ligand catalyst systems were evaluated for the enantioselective hydrogenation of the substrate.

IT 871224-64-5P

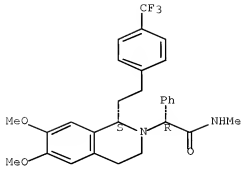
RL: PRPH (Prophetic); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(process for the stereoselective preparation of trisubstituted tetrahydroisoquinoline derivative by using iridium/chiral ligand-catalyzed asym. hydrogenation of the dihydroisoquinoline derivative as the key step)

RN 871224-64-5 CAPLUS

CN 2(1H)-Isoquinolineacetamide, 3,4-dihydro-6,7-dimethoxy-N-methyl-α-phenyl-1-[2-[4-(trifluoromethyl)phenyl]ethyl]-, (αR,1S)- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2009:827320 CAPLUS Full-text
DN 151:123843
TI Process for preparation of (S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)ethyl]-1,2,3,4-tetrahydro-1H-isoquinoline acetate via asymmetric hydrogenation
IN De Vries, Andreas Hendrikus Maria; Domin, Doris; Helms, Matthias; Imboden, Christoph; Koberstein, Ralf; Nazir, Zarghun; Skranc, Wolfgang; Stanek, Michael; Tschebull, Wilhelm; Verzijl, Gerardus Karel Maria
PA Actelion Pharmaceuticals Ltd, Switz.
SO PCT Int. Appl., 36pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2009083903	A1	20090709	WO 2008-IB55509	20081223
	W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
PRAI	WO 2007-IB55334	A	20071228		

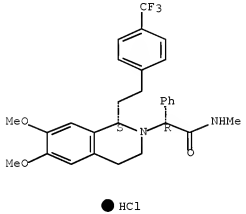
OS CASREACT 151:123843
AB (S)-6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)ethyl]-1,2,3,4-tetrahydro- 1H-isoquinoline acetate was prepared via asym. hydrogenation of 6,7-dimethoxy-1-[2-(4-trifluoromethylphenyl)ethyl]-3,4-dihydro-1H- isoquinoline in the presence of bis(chloro-1,5-cyclooctadieneiridium), (S)-1-dicyclohexylphosphino-2-[(S)-α-(dimethylamino)-2-(dicyclohexylphosphino)benzyl]ferrocene, iodine, and a solvent under 1-200 bar H2. The above reaction was carried out at 5 bar H2 and 30° in CH2Cl2 with a I2/Ir ratio of 2:1 to give the title product in 95% enantiomeric excess with 100% conversion.
IT 913358-93-7P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(preparation of chiral dimethoxytrifluoromethylphenylethyltetrahydroisoquinoline acetate via asym. hydrogenation)

RN 913358-93-7 CAPLUS

CN 2(1H)-Isoquinolineacetamide, 3,4-dihydro-6,7-dimethoxy-N-methyl-α-phenyl-1-[2-[4-(trifluoromethyl)phenyl]ethyl]-, hydrochloride (1:1), (αR,1S)- (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2009:772031 CAPLUS Full-text

DN 151:77937

TI Preparation of tetrahydroisoquinoline derivatives as orexin receptor antagonists

IN Liu, Julie

PA Concert Pharmaceuticals, Inc., USA

SO PCT Int. Appl., 47pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2009079637	A1	20090625	WO 2008-US87477	20081218
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	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	US 20090192188	A1	20090730	US 2008-338754	20081218
PRAI	US 2007-14635P	P	20071218		

OS MARPAT 151:77937
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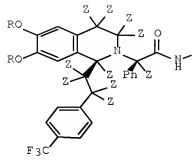

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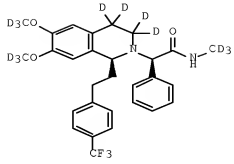


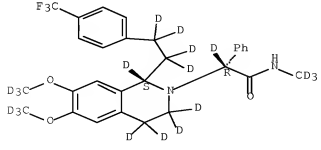
II

AB This title compds. with general formula I [wherein each Z is independently selected from hydrogen or deuterium; each R is independently selected from CD3, CD2H, CDH2, or CH3, and when each R is CH3 then at least one Z is deuterium] or pharmaceutically acceptable salts thereof were prepared as dual OX-1/OX-2 orexin receptor antagonists for the treatment of obesity, bulimia, anorexia nervosa, insomnia, narcolepsy, sleep apnea, jet-lag syndrome, or memory impairment. For example, compound II•HCl was prepared in a multi-step synthesis, with the last step being the condensation of (1S)-[1,2,3,4-tetrahydro-3,3,4,4-d4]-[6,7-dimethoxy-d6]-1-[2-[4-(trifluoromethyl)phenyl]ethyl]-isoquinoline hydrochloride (preparation given) and toluene-4-sulfonic acid [(S)-1-[(methyl-d3)carbamoyl]-1-phenylmethyl] ester (preparation given). The metabolic stability of compds. I has been tested using pooled liver microsomal incubation.

IT 1162658-22-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of tetrahydroisoquinoline derivs. as orexin receptor antagonists)

RN 1162658-22-1 CAPLUS
CN INDEX NAME NOT YET ASSIGNED

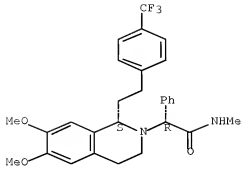
Absolute stereochemistry.



RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2009:541589 CAPLUS Full-text
DN 151:70132
TI Biochemical and behavioural characterization of EMPA, a novel high-affinity, selective antagonist for the OX2 receptor
AU Malherbe, P.; Borroni, E.; Gobbi, L.; Knust, H.; Nettekoven, M.; Pinard, E.; Roche, O.; Rogers-Evans, M.; Wettstein, J. G.; Moreau, J.-L.
CS Discovery Research CNS, F. Hoffmann-La Roche Ltd., Basel, CH-4070, Switz.
SO British Journal of Pharmacology (2009), 156(8), 1326-1341
CODEN: BJPCBM; ISSN: 1476-5381
PB Wiley-Blackwell
DT Journal
LA English
AB The OX2 receptor is a G-protein-coupled receptor that is abundantly found in the tuberomammillary nucleus, an important site for the regulation of the sleep-wake state. Herein, we describe the in vitro and in vivo properties of a selective OX2 receptor antagonist, N-ethyl-2-[(6-methoxy-pyridin-3-yl)-(toluene-2-sulfonyl)-amino]-N-pyridin- 3-ylmethyl-acetamide (EMPA). The affinity of [3H]EMPA was assessed in membranes from HEK293-hOX2-cells using saturation and binding kinetics. The antagonist properties of EMPA were determined by Schild anal. using the orexin-A- or orexin-B-induced accumulation of [3H]inositol phosphates (IP). Quant. autoradiog. was used to determine the distribution and abundance of OX2 receptors in rat brain. The in vivo activity of EMPA was assessed by reversal of [Ala11,D-Leu15]orexin-B-induced hyperlocomotion during the resting phase in mice and the reduction of spontaneous locomotor activity (LMA) during the active phase in rats. [3H]EMPA bound to human and rat OX2-HEK293 membranes with KD values of 1.1 and 1.4 nmol/L-1 resp. EMPA competitively antagonized orexin-A- and orexin-B-evoked accumulation of [3H]IP at hOX2 receptors with pA2 values of 8.6 and 8.8 resp. Autoradiog. of rat brain confirmed the selectivity of [3H]EMPA for OX2 receptors. EMPA significantly reversed [Ala11,D-Leu15]orexin-B-induced hyperlocomotion dose-dependently during the resting phase in mice. EMPA, injected i.p. in rats during the active phase, reduced LMA dose-dependently. EMPA did not impair performance of rats in the rotarod procedure. EMPA is a high-affinity, reversible and selective OX2 receptor antagonist, active in vivo, which should prove useful for anal. of OX2 receptor function.
IT 871224-64-5, Almorexant
RL: PAC (Pharmacological activity); BIOL (Biological study)
(biochem. and behavioral characterization of EMPA)
RN 871224-64-5 CAPLUS
CN 2(1H)-Isoquinolineacetamide, 3,4-dihydro-6,7-dimethoxy-N-methyl-α-phenyl-1-[2-[4-(trifluoromethyl)phenyl]ethyl]-, (αR,1S)- (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2009:457569 CAPLUS Full-text
DN 150:414292
TI Tetrahydroquinoline derivatives for treating post-traumatic stress disorders
IN Jenck, Francois
PA Actelion Pharmaceuticals Ltd., Switz.
SO PCT Int. Appl., 12pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2009047723	A2	20090416	WO 2008-IB54138	20081009
	WO 2009047723	A3	20090528		
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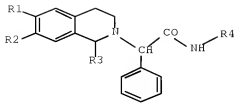
PRAI	WO 2007-IB54130	A	20071010		

OS MARPAT 150:414292
GI



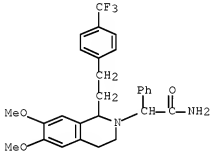
I

AB The invention relates to the use of tetrahydroquinoline derivs. of formula I wherein R1 and R2 each independently represent (C1-C4)alkoxy, R3 represents aryl-(C1-C4)alkyl or heteroaryl-(C1-C4)alkyl, and R4 represents hydrogen or (C1-C4)alkyl, or of pharmaceutically acceptable salts thereof, for the preparation of a medicament for preventing or treating post-traumatic stress disorders.

IT 769171-96-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tetrahydroquinoline derivs. for treating post-traumatic stress disorders)

RN 769171-96-2 CAPLUS

CN 2(1H)-Isoquinolineacetamide, 3,4-dihydro-6,7-dimethoxy-α-phenyl-1-[2-[4-(trifluoromethyl)phenyl]ethyl]- (CA INDEX NAME)



L4 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2007:1227315 CAPLUS Full-text

DN 148:210

TI The hypocretin/orexin receptor: Therapeutic prospective in sleep disorders

AU Nishino, Seiji

CS Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Palo Alto, CA, 94304-5789, USA

SO Expert Opinion on Investigational Drugs (2007), 16(11), 1785-1797
CODEN: EOIDER; ISSN: 1354-3784

PB Informa Healthcare

DT Journal; General Review

LA English

AB A review. The hypocretins (also known as orexins) and their receptors are the focus of many investigators as sites for therapeutic intervention in a number of endocrinol., neurol. and sleep disorders. The interest for the hypocretin system is highlighted by a recent discovery that a human sleep disorder, narcolepsy, is tightly linked with the deficiency of hypocretin peptides. This finding suggests that hypocretin replacement is a promising new

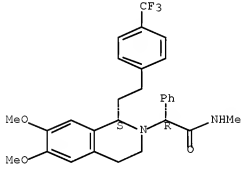
therapeutic intervention for human narcolepsy and related disorders, but this will only become possible when small-mol. (i.e., non-peptide) hypocretin receptor agonists become available. In contrast, high-throughput screening efforts in hypocretin receptor drug discovery programs by a number of pharmaceutical companies have already identified novel small-mol. hypocretin receptor antagonists and these antagonists may be used for the treatment of insomnia, especially for sleep-initiation problems. This is because hypocretin-deficient narcoleptic subjects show very short sleep latency and the blockade of the hypocretin receptor may induce a similar sleep symptom. At least two hypocretin receptor antagonists (ACT-078573 and GW-649868) are presently under development for the treatment of human insomnia and the promising aspects and limitations of these therapeutic interventions are discussed in this paper.

IT 871224-64-5, ACT-078573
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hypocretin/orexin receptor and therapeutic prospective in sleep disorders)

RN 871224-64-5 CAPLUS

CN 2(1H)-Isoquinolineacetamide, 3,4-dihydro-6,7-dimethoxy-N-methyl-α-phenyl-1-[2-[4-(trifluoromethyl)phenyl]ethyl]-, (αR,1S)- (CA INDEX NAME)

Absolute stereochemistry.



OSC.G 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2007:1064566 CAPLUS Full-text
DN 147:357218
TI Tetrahydroisoquinoline derivatives to enhance memory function
IN Jenck, Francois
PA Actelion Pharmaceuticals Ltd., Switz.
SO PCT Int. Appl., 37pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2007105177	A1	20070920	WO 2007-IB50868	20070314
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,				

GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

AU	2007226203	A1	20070920	AU 2007-226203	20070314
CA	2644010	A1	20070920	CA 2007-2644010	20070314
EP	1998774	A1	20081210	EP 2007-735108	20070314

R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS

MX	2008011647	A	20080922	MX 2008-11647	20080911
CN	101400348	A	20090401	CN 2007-80009113	20080912
US	20090082394	A1	20090326	US 2008-293031	20080915
NO	2008004253	A	20081010	NO 2008-4253	20081010
KR	2008103597	A	20081127	KR 2008-724936	20081013
IN	2008CN05547	A	20090320	IN 2008-CN5547	20081015
PRAI	WO 2006-IB50812	A	20060315		
	WO 2007-IB50868	W	20070314		

OS MARPAT 147:357218

AB The invention relates to the use of tetrahydroisoquinoline derivs. for the preparation of a medicament to enhance, maintain and/or restore all stages and/or types of short-, middle- and/or long-term memory.

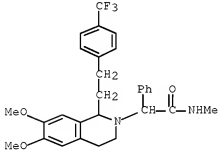
IT 871224-62-3

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(tetrahydroisoquinoline derivs. to enhance memory function)

RN 871224-62-3 CAPLUS

CN 2(1H)-Isoquinolineacetamide, 3,4-dihydro-6,7-dimethoxy-N-methyl-α-phenyl-1-[2-[4-(trifluoromethyl)phenyl]ethyl]- (CA INDEX NAME)



RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2007:148782 CAPLUS Full-text

DN 147:2295

TI Promotion of sleep by targeting the orexin system in rats, dogs and humans

AU Brisbare-Roch, Catherine; Dingemanse, Jasper; Koberstein, Ralf; Hoever, Petra; Aissaoui, Hamed; Flores, Susan; Mueller, Celia; Nayler, Oliver; van

Gerven, Joop; de Haas, Sanne L.; Hess, Patrick; Qiu, Changbin; Buchmann, Stephan; Scherz, Michael; Weller, Thomas; Fischli, Walter; Clozel, Martine; Jenck, Francois

CS Research and Development, Actelion Pharmaceuticals Ltd., Allschwil, CH-4123, Switz.

SO Nature Medicine (New York, NY, United States) (2007), 13(2), 150-155
CODEN: NAMEFI; ISSN: 1078-8956

PB Nature Publishing Group

DT Journal

LA English

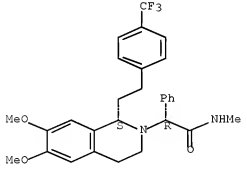
AB Orexins are hypothalamic peptides that play an important role in maintaining wakefulness in mammals. Permanent deficit in orexinergic function is a pathophysiol. hallmark of rodent, canine and human narcolepsy. Here we report that in rats, dogs and humans, somnolence is induced by pharmacol. blockade of both orexin OX1 and OX2 receptors. When administered orally during the active period of the circadian cycle, a dual antagonist increased, in rats, electrophysiol. indexes of both non-REM and, particularly, REM sleep, in contrast to GABAA receptor modulators; in dogs, it caused somnolence and increased surrogate markers of REM sleep; and in humans, it caused subjective and objective electrophysiol. signs of sleep. No signs of cataplexy were observed, in contrast to the rodent, dog or human narcolepsy syndromes. These results open new perspectives for investigating the role of endogenous orexins in sleep-wake regulation.

IT 871224-64-5, ACT 078573
RL: PAC (Pharmacological activity); BIOL (Biological study)
(sleep promotion by targeting orexin system in rats and dogs and humans)

RN 871224-64-5 CAPLUS

CN 2(1H)-Isoquinolineacetamide, 3,4-dihydro-6,7-dimethoxy-N-methyl-α-phenyl-1-[2-[4-(trifluoromethyl)phenyl]ethyl]-, (αR,1S)- (CA INDEX NAME)

Absolute stereochemistry.



OSC.G 35 THERE ARE 35 CAPLUS RECORDS THAT CITE THIS RECORD (37 CITINGS)
RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN

AN 2005:1313838 CAPLUS Full-text

DN 144:51461

TI Preparation of substituted 1,2,3,4-tetrahydroisoquinolines as orexin receptor antagonists

IN Weller, Thomas; Koberstein, Ralf; Aissaoui, Hamed; Clozel, Martine; Fischli, Walter

PA Actelion Pharmaceuticals Ltd, Switz.
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005118548	A1	20051215	WO 2005-EP1879	20050223
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
	RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2005250077	A1	20051215	AU 2005-250077	20050223
	CA 2557163	A1	20051215	CA 2005-2557163	20050223
	EP 1751111	A1	20070214	EP 2005-804734	20050223
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	CN 1926109	A	20070307	CN 2005-80006491	20050223
	BR 2005008263	A	20070731	BR 2005-8263	20050223
	JP 2007525531	T	20070906	JP 2007-501172	20050223
	JP 4094050	B2	20080604		
	ZA 2006006974	A	20080430	ZA 2006-6974	20060821
	MX 2006009833	A	20061030	MX 2006-9833	20060829
	US 20070191424	A1	20070816	US 2006-598449	20060830
	NO 2006004347	A	20060926	NO 2006-4347	20060926
	IN 2006CN03637	A	20070615	IN 2006-CN3637	20060928
	KR 2006123785	A	20061204	KR 2006-720299	20060929
	KR 848747	B1	20080725		
PRAI	WO 2004-EP2020	A	20040301		
	WO 2005-EP1879	W	20050223		

OS CASREACT 144:51461; MARPAT 144:51461
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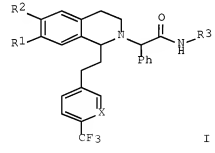

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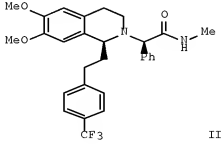


II

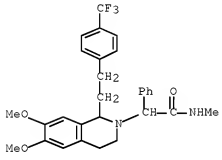
AB Title compds. I [R1-2 = H, alkoxy; R3 = alkyl; X = CH, N] are prepared For instance, II is prepared from a Ru-catalyzed enantioselective alkylation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline with 1-bromomethyl-4-

trifluoromethylbenzene followed by alkylation of the resulting isoquinoline with (S)-α-(4-toluenesulfonyloxy)-N- methylphenylacetamide (preparation given). Compds. of the invention are orexin antagonists with activity in the nanomolar range. I are useful for the treatment of, e.g., anxiety and depression.

IT 871224-62-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of substituted 1,2,3,4-tetrahydroisoquinolines as orexin receptor antagonists)

RN 871224-62-3 CAPLUS

CN 2(1H)-Isoquinolineacetamide, 3,4-dihydro-6,7-dimethoxy-N-methyl-α-phenyl-1-[2-[4-(trifluoromethyl)phenyl]ethyl]- (CA INDEX NAME)



OSC.G 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2004:817867 CAPLUS Full-text
DN 141:314172
TI Preparation of tetrahydroisoquinolyl acetamide derivatives for use as orexin receptor antagonists
IN Aissaoui, Hamed; Clozel, Martine; Weller, Thomas; Koberstein, Ralf; Sifferlen, Thierry; Fischli, Walter
PA Actelion Pharmaceuticals Ltd., Switz.
SO PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004085403	A1	20041007	WO 2004-EP3057	20040323
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	RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,				

	TD, TG				
	AU 2004224156	A1	20041007	AU 2004-224156	20040323
	CA 2518945	A1	20041007	CA 2004-2518945	20040323
	EP 1611104	A1	20060104	EP 2004-722563	20040323
	EP 1611104	B1	20090701		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
	BR 2004008681	A	20060328	BR 2004-8681	20040323
	CN 1764647	A	20060426	CN 2004-80007856	20040323
	CN 100432056	C	20081112		
	JP 2006521323	T	20060921	JP 2006-504816	20040323
	RU 2345985	C2	20090210	RU 2005-132961	20040323
	AT 435210	T	20090715	AT 2004-722563	20040323
	US 20060178515	A1	20060810	US 2005-549180	20050916
PRAI	WO 2003-EP3143	A	20030326		
	WO 2004-EP3057	W	20040323		

OS CASREACT 141:314172; MARPAT 141:314172

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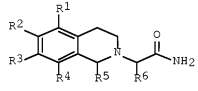

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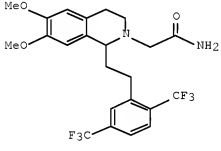


II

AB Title compds. I [R1-4 = H, CN, halo, etc.; R5 = (un)substituted Ph, naphthyl, etc.; R6 = H, substituted Ph, etc.] are prepared For instance, II was prepared by cyclization of 3-[2,5-bis(trifluoromethyl)phenyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]propanamide and subsequent alkylation with 2-bromoacetamide. Compds. of the invention have IC50 of 1 to 100 nM for the orexin-1 (OX1) and OX2 receptor. Compds. I are useful for the treatment of, e.g., asthma.

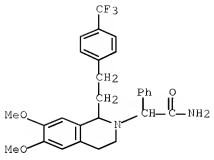
IT 769171-96-2P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of tetrahydroisoquinolyl acetamide derivs. for use as orexin receptor antagonists)

RN 769171-96-2 CAPLUS

CN 2(1H)-Isoquinolineacetamide, 3,4-dihydro-6,7-dimethoxy-α-phenyl-1-[2-[4-(trifluoromethyl)phenyl]ethyl]- (CA INDEX NAME)



OSC.G 6 THERE ARE 6 CAPLUS RECORDS THAT CITE THIS RECORD (6 CITINGS)
RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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STN INTERNATIONAL LOGOFF AT 16:26:11 ON 18 AUG 2009